Doc 12

PATENT SPECIFICATION

1,140,387

NO DRAWINGS

1,140,387

Date of Application and filing Complete Specification: 15 July, 1966.

No. 31938/66.

Application made in Germany (No. T29055 IVd/12p) on 23 July, 1965.

Complete Specification Published: 15 Jan., 1969.

Index at acceptance:—C2 C(1F1B, 1FD3, 1H1A1, 1H1C3, 1J1A3, 1J1A4, 1J1A6, 1J1A9, 1J1B, 1J1C2, 1JC3, 1J1E, 1J1Z, 2A3, 2A5, 2A9, 2B43D1, 2B43D3, 2B43G1, 2B50D3, 2B50G1, 2D6, 2D43A, 2D43C, 2D43D, 2D43F, 2D43J, 2D43L, 2D43S4, 2R15, 2R16, 2R17, 2T21, B4A1, B4A4, B4D, B4E, B4H, B4M, LE29X, LE29Y, LE32Y, LE36Y, LE214, LE256, LE305, LE321, LE364, LE670, LH29X, LH29Y, LH32Y, LH36Y, LH214, LH220, LH256, LH305, LH321, LH364, LH662, LH670, LH680, LH682, LL29X, LL29Y, LL214, LL220, LL225, LL256, LL305, LL321, LL351, LL355, LL670, LL675); A5 B(1R1, 1S, 2R1, 2S)

Int. Cl.:—C 07 d 99/10

COMPLETE SPECIFICATION

ERRATA

SPECIFICATION No. 1,140,387

Page 1, Index at acceptance:—*for* "1JC3" *read* "1J1C3"
Page 2, line 21, *for* "p" *read* "*p*"
Page 3, line 92, *for* "C 55.5% H 6.79%" *read* "C 55.4% H 6.72%"
Page 4, Example 5, *for* "thiouresa" *read* "thiourea"
Page 5, Example 10, *for* "4,5,67" *read* "4,5,6,7."
Page 5, Example 10, *for* "104°C" *read* "106°C"
Page 6, Example 12, *for* "4,5,6,-7-" *read* "4,5,6,7-"
Page 7, Example 16, *for* "(Calc:" *read* "Calc:"
Page 7, Example 17, *for* "dinhydrochloride" *read* "dihydrochloride"
Page 7, Example 18, *for* "—A—" *read* "—A"
Page 10, Example 31, *for* "sulphonamide" *read* "sulphonamido"
Page 12, Example 44, *after* "and N" *insert* hyphen
Page 13, Example 46, *for* "4,5,6,-7-" *read* "4,5,6,7-"
Page 13, Example 49, *for* "4,5,6,-7-" *read* "4,5,6,7-"
Page 14, Example 51, *for* "2-*p*-" *read* "2-*o*-"
Page 14, Example 52, *for* "2-*o*-" *read* "2-*p*-"
Page 14, Example 53, *for* "N-(2-" *read* "N-(2,4-"
Page 15, Example 56, *for* "Dimethybenzenesulphonamido" *read* "Dimethoxybenzenesulphonamido"
Page 15, Example 57, *for* "[5,4,4-c]" *read* "[5,4-c]"
Page 19, Example 76, *for* "tertahydro" *read* "tetrahydro"
Page 19, Example 73, *after* "thiazolo" *delete* "-[" and *substitute* "[5,4-c]"
Page 21, Example 89, *for* "dimethyloxybenzenesulphonylthiourea" *read* "dimethoxybenzenesulphonylthiourea"
Page 22, Example 92, *for* "ethy'" *read* "ethyl"
Page 22, Example 93, *for* "hemidhydrate" *read* "hemihydrate"
Page 22, Example 94, *after* "[5,4-c]-" *delete* "$>$"
Page 22, Example 95, *for* "-5-α-[phenylethyl]" *read* "-5-[α-phenyl-ethyl]"
Page 22, Example 95, *for* "$C_{21}H_{25}N_3S_4O_3$" *read* "$C_{21}H_{23}N_3O_4S_3$"
Page 22, Example 95, *after* "(from 1" *insert* hyphen
Page 23, Example 96, *for* "methoxybenzenesyulphonyl" *read* "methoxybenzenesulphonyl"
Page 23, Example 97, *for* "Tetramethlenimino" *read* "Tetramethylenimino"
Page 25, line 10, *for* "Sugar" *read* "sugar"
Page 30, line 9, *for* "0.04 g" *read* "0.4 g"
Page 31, line 8, *for* "pyridimidine" *read* "pyrimidine"
Page 31, line 31, *for* "Codein" *read* "Codeine"
Individual letters, e.g. "*p*" and "*m*" should be shown in italics throughout Specification

THE PATENT OFFICE
17th February 1969

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Int. Cl.:—C 07 d 99/10

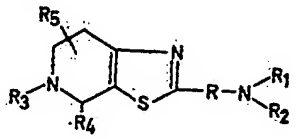
COMPLETE SPECIFICATION

4,5,6,7-Tetrahydro-Thiazolo-[5,4-c]Pyridines

We, Dr. KARL THOMAE, G.M.B.H., a German Body Corporate of Biberach an der Riss, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new 4,5,6,7-tetrahydro - thiazolo - [5,4-c] pyridines having valuable physiological properties.

According to the present invention we provide compounds of the general formula:—

I 

[in which R_1 represents a hydrogen atom, an alkyl radical having 1—6 carbon atoms, an alkenyl radical having 2—6 carbon atoms which may be substituted with halogen, a cycloalkyl radical having 3—8 carbon atoms, an aryl radical having 6—10 carbon atoms, an aralkyl radical having 7—9 carbon atoms, an acyl radical derived from an aliphatic or aromatic carboxylic acid or sulphonic acid, a carbamoyl radical or an amidino radical;

R_2 represents a hydrogen atom, an alkyl radical having 1—6 carbon atoms, an alkenyl radical which has 2—6 carbon atoms and may be substituted with a halogen atom, a cycloalkyl radical or, together with the nitrogen atom and R_1, forms a heterocyclic ring which may be interrupted by a further hetero atom and/or substituted by a hydroxyl group, a methyl or a phenyl group;

R_3 represents a hydrogen atom, an alkyl radical having 1—6 carbon atoms, an alkenyl radical having 2—6 carbon atoms which may be substituted with a halogen atom, a cycloalkyl radical having 3—8 carbon atoms, an aryl radical having 6—10 carbon atoms or an aralkyl radical having 7—9 carbon atoms, an acyl radical derived from an aliphatic or aromatic carboxylic acid or sulphonic acid, or a carbamoyl, thiocarbamoyl or amidino radical; and, where at least one of the groups R_1, R_2 and R_3 represents an alkyl group, said group may be substituted by a hydroxyl, alkoxy, aryloxy or cycloalkyl group, or a carboxyl, carbalkoxy or an amido radical; and, where at least one of the groups R_1, R_2 and R_3 represents an aromatic group, said group may be substituted by halogen atoms, hydroxyl, alkyl, alkoxy, alkylthio, alkylsulphonyl, alkylene dioxy, amino, alkylamino, acylamino or aminosulphonyl groups;

R_4 and R_5, which may be the same or different, represent hydrogen atoms, alkyl groups with 1 to 3 carbon atoms, aryl or aralkyl radicals, and R represents a carbon-nitrogen bond or a divalent aliphatic hydrocarbon radical having 1 to 3 carbon atoms] and their physiologically acceptable salts of inorganic and organic acids.

As stated above, the 4,5,6,7 - tetrahydro-thiazolo-[5,4-c] pyridines and their salts have valuable physiological properties. In particular they exhibit analgesic, antitussive, sedative, antipyretic and antiphlogistic activity.

Preferred compounds of general formula I by virtue of their good sedative activity are

[*Pr*

SEE ERRATA SLIP ATTACHED

those which contain a free amino or mono- or dialkylamino group in the 2-position and an alkyl group in the 5-position, these compounds also have good antipyretic and antiphlogistic activity. Preferred compounds of general formula I having good analgesic properties are those in which R_1 or R_2 represents an acyl group derived from a sulphonic acid, particularly a benzenesulphonyl group.

Particularly preferred compounds of formula I by virtue of their especially valuable physiological properties are as follows:—

2 - amino - 4,5,6,7 - tetrahydro - thiazolo-[5,4-c]pyridine,

2 - amino - 5 - methyl - 4,5,6,7 - tetrahydro-thiazolo[5,4-c]pyridine,

2 - amino - 5 - ethyl - 4,5,6,7 - tetrahydro-thiazolo[5,4-c]pyridine,

2 - amino - 5 - propyl - 4,5,6,7 - tetrahydro-thiazolo[5,4-c]pyridine,

2 - *p* - toluenesulphonamido - 5 - ethyl-4,5,6,7 - tetrahydro - thiazolo[5,4 - c]pyridine,

2 - [2,4 - dibromobenzenesulphonamido] - 5 - ethyl - 4,5,6,7 - tetrahydro-thiazolo[5,4-c]-pyridine,

2 - *p* - toluenesulphonamido - 5 - (phenyl-ethyl) - 4,5,6,7 - tetrahydro - thiazolo-[5,4-c]pyridine,

2 - *p* - methoxybenzenesulphonamido - 5 - (phenyl - ethyl) - 4,5,6,7 - tetrahydro - thiazolo[5,4-c]pyridine,

2 - *p* - bromobenzenesulphonamido - 5 - (phenyl - ethyl) - 4,5,6,7 - tetrahydro - thiazolo[5,4-c]pyridine,

2 - [2,4 - dibromobenzenesulphonamido] - 5 - (phenyl - ethyl) - 4,5,6,7 - tetrahydro - thiazolo[5,4-c]pyridine,

2 - [3,4 - dimethoxybenzenesulphonamido]-5 - (phenyl - ethyl) - 4,5,6,7 - tetrahydro-thiazolo[5,4-c]pyridine,

2 - ethylamino - 5 - propyl - 4,5,6,7 - tetrahydro - thiazolo[5,4-c]pyridine,

2 - propylamino - 5 - propyl - 4,5,6,7 - tetrahydro - thiazolo[5,4-c]pyridine, and

2 - allylamino - 5 - propyl - 4,5,6,7 - tetrahydro - thiazolo[5,4-c]pyridine.

Compounds of formula I may conveniently be used in the form of their physiologically acceptable acid addition salts. Examples of acids suitable for the preparation of these salts include hydrochloric, hydrobromic, sulphuric, phosphoric, succinic, tartaric, citric, adipic, maleic and fumaric acids. However, the hydrochlorides of the compounds of formula I are particularly preferred as acid addition salts. These salts may be mono-, di- or tri- acid addition salts.

According to a further feature of the invention we provide pharmaceutical compositions comprising, as active ingredient, at least one of the compounds according to the invention in association with a pharmaceutical carrier or excipient. The compositions may be presented in a form suitable for oral, rectal or parenteral administration. Thus for example, compositions for oral administration may be solid or liquid and may take the form of capsules, tablets, dragees, drop solutions or syrups, such compositions comprising carriers or excipients conveniently used in the pharmaceutical art. Thus, suitable tabletting excipients include lactose, potato and maize starches, talc, gelatine, stearic and silicic acids, magnesium stearate and polyvinylpyrrolidone.

For parenteral administration, the carrier or excipient may be a sterile, parenterally acceptable liquid, e.g., pyrogen-free water, or an aqueous solution of polyvinylpyrrolidone, or a parenterally acceptable oil, e.g., arachis oil. The compositions may be presented as injectable solutions or suspensions contained in ampoules or multi-dose flasks.

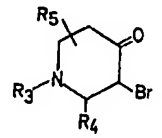
In compositions for rectal administration, the carrier may comprise a suppository base, e.g. cocoa butter or another glyceride.

Advantageously, the compositions may be formulated as dosage units, each unit supplying of fixed dose of active ingredient. Dragees, capsules, depot-dragees, suppositories and ampoules are examples of preferred dosage unit forms of the compositions according to the invention. For adults, each dosage unit may conveniently contain 0.5 to 20 mg, preferably 1 to 10 mg, of active ingredient; the usual dosage unit containing 5 mg. of active ingredient. The average daily dosage for adults is 15 to 60 mg. of active compound, depending on the route of administration.

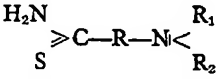
For administering the active compounds to children and babies the dosage units will be smaller, e.g., for children the usual dosage may conveniently contain 0.5 to 5 mg., preferably 1 to 2 mg, of active ingredient, the usual dosage unit containing 1 mg. of active ingredient, while for babies each dosage unit may conveniently contain 0.1 to 2 mg, preferably 0.5 to 1 mg. of active ingredient.

According to the present invention we also provide compositions as described above which contain as active ingredients, one or more further substances having analgesic, anti-inflammatory, anti-tussive, coronary-dilating or heart-stimulant activity, in addition to the compounds of general formula I and their salts. Suitable further active ingredients include butazolidine, 1 - (*p* - chlorophenyl)-2,3 - dimethyl-4-dimethylamino - butanol-(2) hydrochloride, codein phosphate, 2,6 - bis-(diethanolamino) - 4,8 - dipiperidino - pyrimido - [5,4 - d]pyrimidine, digoxine and dolantin (registered Trade Mark).

According to a further feature of the invention we provide a process for the preparation of compounds of general formula I (as hereinbefore defined) which comprises reacting a hydrohalic acid salt of a 3 - bromo - piperidone - (4) of the formula

II 

(in which R_3, R_4 and R_5 are as hereinbefore defined) with a substituted thiourea or thioamide of the formula

 III

(in which R_1, R_2 and R are as hereinbefore defined).

The reaction is advantageously carried out in the presence of an inert solvent at temperatures between ambient temperature and the boiling point of the solvent used, if desired in the presence of an acid binding agent. Suitable solvents include water, aliphatic alcohols or mixtures thereof or aromatic hydrocarbons. Suitable acid binding agents include inorganic bases such as sodium carbonate or potassium carbonate or tertiary organic bases such as triethylamine or pyridine; the latter may, if used in excess, at the same time serve as the solvent for the reaction. However, the reaction may also be carried out in the absence of a solvent, simply by melting the reactants together. The 3-bromo-piperidone is conveniently in the form of its hydrobromide.

The compounds obtained by this process may, if desired, be converted by conventional methods into their physiologically acceptable acid addition salts by treatment with an inorganic or organic acid. Suitable acids for this purpose are, for example, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, succinic acid, tartaric acid, citric acid, adipic acid, maleic acid or fumaric acid.

In cases where compounds of formula I are obtained in which R_3 is an acyl radical of an aliphatic or aromatic carboxylic acid and R_1 is not an acyl radical of an aliphatic or aromatic carboxylic acid, these compounds may, if desired, subsequently be converted by known saponification methods into corresponding compounds in which R_3 represents a hydrogen atom. Conversely compounds in which R_3 represents a hydrogen atom may, if desired, be subsequently converted by conventional methods into compounds of formula I in which R_3 has one of the meanings as hereinbefore defined with the exception of an aryl radical and a hydrogen atom; e.g. by reacting them with an alkylating, alkenylating, cycloalkenylating, aralkylating, acylating, carbamoylating, thiocarbamoylating or amidinating agent.

Some of the bromopiperidones of formula II used as starting materials are known in the literature while the others can be prepared by conventional methods [Chem. Abstr. *58*, 12.544 b or Houben Weyl, Methoden der organischen Chemie, Volume *5/4* 171 (1960)], for example, by brominating the substituted piperidone-(4)-hydrobromides in glacial acetic acid. The compounds of formula II thus obtained need not be isolated but can be reacted direct in the form of a crude reaction mixture with a compound of formula III. The thioureas and thioamides of formula III used in the reaction are either known from the literature or obtainable by conventional methods [Houben Weyl, Methoden der organischen Chemie, Volume 9, 762—768, 884—89 (1955)].

For the better understanding of the invention the following examples are given by way of illustration only.

EXAMPLE 1

2-Amino-5-allyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine

29.9 g. (0.1 mol) of 1-allyl-3-bromo-piperidone-4-hydrobromide (m.p. = 100°C) are heated with 7.6 g. (0.1 mol) of thiourea in 50 cc of water for 2½ hours at 60°C, during which time the pH of the reaction solution remains constant at 1—2. After cooling, the acidic reaction solution is shaken three times with 50 cc portions of chloroform to remove any by-products formed by the reaction. The aqueous phase is made strongly alkaline with 35% sodium hydroxide solution, whereby the reaction product separates out in a crystalline form. The crude product is recrystallised from 100 cc of isopropanol with the aid of active charcoal.

Yield 17.0 g. (87% of theory) M.pt. = 97°C.
Calculated: C 55.5% H 6.79%.
Found: C 55.5% H 6.79%.

EXAMPLE 2

2-*p*-Bromobenzene-sulphonamido-5-ethyl-4,5,6,7-tetrahydro-thiazolo-[5,4-c] pyridine hydrochloride

5.74 g. (0.02 mol) of 1-ethyl-3-bromo-piperidone-(4) hydrobromide are added in portions to a pyridine solution of 5.9 g. (0.02 mol) of *p*-bromobenzene-sulphonylthiourea (m.p. 183—184°C, prepared by reacting *p*-bromobenzene-sulphonic acid chloride with disodium cyanamide in aqueous solution to form sodium *p*-bromo-benzene-sulphonyl-cyanamide, followed by the addition of hydrogen sulphide by means of a solution of sodium thiosulphate saturated with sulphur dioxide) the reaction mixture is then heated on a boiling water bath for 15 minutes and the pyridine distilled off *in vacuo*. The oily residue after drying is triturated with 20 cc of ethanol, the reaction product crystallising out in the form of its hydrobromide. The base is liberated from this crude product by means of sodium hydroxide solution and can be converted by treatment with hydrochloric acid

into its hydrochloride which is then recrystallised from a methanol/water mixture in the ratio of 1:5. Yield 4.2 g, (48% of theory)

M.p. =250°C (decomposition).
Calculated: C 38.3% H 3.90%
Found: C 37.8% H 4.07%

EXAMPLE 3

2 - *p* - Toluenesulphonamido - 5 - amyl - 4,5,6,7 - tetrahydro - thiazolo[5,4 - c]-pyridine hydrochloride

10 g. (0.03 mol) of 1 - amyl - 3 - bromo-piperidone - (4) hydrobromide (m.p. 100—103°C) are dissolved in 30 cc of pyridine, and 6.9 g. (0.03 mol) of *p*-toluenesulphonyl thiourea are then added in portions to this solution. The reaction mixture is then heated on a water bath for 15 minutes. 30 cc of ethanol and 100 cc of water are then added to the reaction mixture and the mixture acidified with concentrated hydrochloric acid. The reaction product, after being precipitated and separated by suction filtration, is recrystallised from methanol with the aid of active charcoal.

Yield: 6.5 g. (51% theory)
M.p. =238°C (decomposition).
Calculated: C 51.8% H 6.29%
Found: C 51.5% H 6.31%

The compounds listed hereinafter were prepared by the same process from 3 - bromo-piperidone-(4) hydrobromide or its derivatives substituted in the 1-position and the corresponding compound of formula III; in the following examples the bromo-piperidone is in all cases indicated by A, any substituent in the 1-position being written as a prefix.

EXAMPLE 4

2-Amino-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dihydrochloride

M.p. 269 — 270°C. $C_6H_9N_3S.2HCl$

Calculated: C 31.6% H 4.64%

Found: C 31.9% H 4.79%

(from 1-benzoyl-A and thiourea followed by saponification of the resulting 2-amino-5-benzoyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine with 10% hydrochloric acid).

EXAMPLE 5

2-Amino-5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine

M pt. 171 — 173°C $C_7H_{11}N_3S$

Calc.: C 49.7% H 6.55%

Found: C 49.4% H 6.51%

(from 1-methyl-A and thiouresa)

EXAMPLE 6

2-Amino-5-ethyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine

M.pt. 102 — 106°C $C_8H_{13}N_3S$

Calc.: C 52.5% H 7.15%

Found: C 52.2% H 7.15%

(from 1-ethyl-A and thiourea)

EXAMPLE 7

2-Amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine
M.pt. 74 — 76°C $C_9H_{15}N_3S$

Calc.: C 54.9% H 7.68%

Found: C 54.6% H 7.74%

(from 1-propyl-A and thuiourea)

Dihydrochloride: m.pt. 235 — 236°C. $C_9H_{15}N_3S \cdot 2HCl$

Calc.: C 40.0% H 6.36%

Found: C 40.0% H 6.59%

EXAMPLE 8

2-Amino-5-isopropyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine

M.pt. 104 — 105°C $C_9H_{16}N_3S$

Calc.: C 54.9% H 7.68%

Found: C 55.1% H 8.09%

(from 1-isopropyl-A and thiourea)

EXAMPLE 9

2-Amino-5-butyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine

M.pt. 80°C $C_{10}H_{17}N_3S$

Calc.: C 56.9% H 8.13%

Found: C 56.8% H8.10%

(from 1-butyl-A and thiourea)

EXAMPLE 10

2-Amino-5-isobutyl-4,5,67-tetrahydro-thiazolo[5,4-c]pyridine

M.pt 104 — 104°C $C_{10}H_{17}N_3S$

Calc.: C 56.9% H 8.13%

Found: C 57.1% H 8.36%

(from 1-isobutyl-A and thiourea)

EXAMPLE 11

2-Amino-5-amyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine

M.pt. 76 — 80°C $C_{11}H_{19}N_3S$

Calc.: C 58.7% H 8.50%

Found: C 59.0% H 8.47%

(from 1-amyl-A and thiourea)

EXAMPLE 12

2-Amino-5-cyclohexyl-4,5,6,-7-tetrahydro-thiazolo[5,4-c]pyridine

M.pt. 177°C $C_{12}H_{19}N_3S$

Calc.: C 60.8% H 8.08 %

Found: C 60.4% H 7.96%

(from 1-cyclohexyl-A and thiourea)

EXAMPLE 13

2-Amino-5-benzyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dihydrochloride

M.pt. 220°C $C_{13}H_{15}N_3S \cdot 2HCl$

Found: C 49.1% H 5.38%

Calc.: C 49.3% H 5.65%

EXAMPLE 14

2-Amino-5-phenyl-ethyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine

M.pt 180°C $C_{14}H_{17}N_3S$

Found: C 64.9% H 6.62%

Calc.: C 64.7% H 6.58%

(from 1-phenyl-ethyl-A and thiourea)

EXAMPLE 15

2-Amino-5-benzoyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine

M.pt. 225 — 227°C $C_{14}H_{15}N_3S$

Found: C 60.3% H 5.05%

Calc.: C 60.0% H 5.13%

(from 1-benzoyl-A and thiourea)

EXAMPLE 16

2-Amino-4,5,6-trimethyl-4,5,6,7-tetrahydro-thiazolo[5,4,-c]-pyridine

M.pt. 184 — 185°C $C_9H_{15}N_3S$

Found: C 54.7% H 7.65%

(Calc: C 54.8% H 7.66%

(from 1,2,6-Trimethyl-3-bromopiperidone-(4)-hydrobromide and thiourea)

EXAMPLE 17

2-Amino-5-methyl-4,6-diphenyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dinhydrochloride

M.pt. 219 — 220°C $C_{19}H_{19}N_3S \cdot 2HCl$

Calc.: C 57.9 % H 5.36%

Found: C 57.8% H 5.48%

(1-methyl-2,6-diphenyl-3-bromo-piperidone-(4)-hydrobromide and thiourea)

EXAMPLE 18

2-Methylamino-5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine

M.pt. 137 — 139°C $C_8H_{13}N_3S$

Calc.: C 52.5% H 7.15%

Found: C 52.6% H 7.38%

(from 1-methyl-A- and N-methyl thiourea)

EXAMPLE 19

2-Ethylamino-5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]-pyridine dihydrochloride

M.pt. 224 — 225°C $C_9H_{15}N_3S \cdot 2HCl$

Calc.: C 40.0% H 6.34%

Found: C 40.0% H 6.41%

(from 1-methyl-A and N-ethylthiourea)

EXAMPLE 20

2-Butylamino-5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]-pyridine dihydrochloride

M.pt. 221 — 222°C $C_{11}H_{19}N_3S \cdot 2HCl$

Calc.: C 44.3% H 7.10%

Found: C 44.2% H 7.14%

(from 1-methyl-A and N-butylthiourea)

EXAMPLE 21

2-Allylamino-5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]-pyridine dihydrochloride

M.pt. 203 — 207°C $C_{10}H_{15}N_3S$. 2HCl

Calc.: C 42.6% H 6.07%

Found: C 42.6% H 6.17%

(from 1-methyl-A and N-allyl -thiourea)

EXAMPLE 22

2-Phenylamino-5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]-pyridine dihydrochloride

M.pt. 223 — 224°C $C_{13}H_{15}N_3S$. 2HCl

Calc.: C 49.1% H 5.38%

Found: C 49.4% H 5.59%

(from 1-methyl-A and N-phenyl-thiourea)

EXAMPLE 23

2-Butylamino-5-allyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine

M.pt. 49 — 50°C $C_{13}H_{21}N_3S$

Calc.: C 62.2% H 8.30%

Found: C 61.7% H 8.37%

(from 1-allyl-A and N-butyl-thiourea)

EXAMPLE 24

2-Ethylamino-5-phenylethyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]-pyridine dihydrochloride

M.pt. 225°C $C_{16}H_{21}N_3S$ 2.HCl.$2H_2O$

Calc.: C 48.5% H 6.85%

Found: C 48.9% H 6.95%

(from 1-phenyl-ethyl-A and N-ethyl-thiourea)

EXAMPLE 25

2-Butylamino-5-(phenyl-ethyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine

M.pt. 84 — 85°C $C_{18}H_{25}N_3S$

Calc.: C 68.6% H 7.95%
Found: C 68.4% H 7.76%

(from 1-phenyl-ethyl-A and N-butyl-thiourea)

EXAMPLE 26

2-Allylamino-5-(phenyl-ethyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]-pyridine dihydrochloride

M.pt. 221°C $C_{17}H_{21}N_3S$ 2HCl .$2H_2O$

Calc.: C 50.1% H 6.55%

Found: C 50.6% H 6.32%

(from 1-phenyl-ethyl-A and N-allyl-thiourea)

EXAMPLE 27

2-Morpholino-5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]-pyridine dihydrochloride

M.pt. 220 — 221°C $C_{11}H_{17}N_3OS.2HCl$

Calc.: C 49.7% H 6.55%

Found: C 49.3% H 6.51%

(from 1-methyl-A and N-thiocarbamoyl-morpholine)

EXAMPLE 28

2-Morpholino-5-(phenyl-ethyl) 4,5,6,7-tetrahydro-thiazolo[5,4-c]-pyridine dihydrochloride

M.pt. 217°C $C_{18}H_{23}N_3OS.2HCl$

Calc.: C 49.2% H 6.60%

Found: C 48.4% H 6.10%

(from1-phenyl-ethyl-A and N-thiocarbamoyl-morpholine)

EXAMPLE 29

2-Acetamido-5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]-pyridine hydrochloride

M.pt. 166 — 167°C $C_9H_{13}N_3OS.HCl$

Calc.: C 38.0% H 5.32%

Found: C 37.7% H 5.69%

(from 1-methyl-A and N-acetyl-thiourea)

EXAMPLE 30

2-Benzamido-5-allyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]-pyridine hydrochloride

M.pt. 233°C $C_{16}H_{17}N_3OS.HCl$

Calc.: C 57.2% H 5.30%

Found: C 56.8% H 5.50%

(from 1-allyl-A and N-benzoyl-thiourea)

EXAMPLE 31

2-p-Toluene sulphonamide-5-methyl-4,5,6,7-tetrahydro-thiazolo-[5,4-c]-pyridine dihydrochloride

M.pt.: 258 — 260°C $C_{14}H_{17}N_3O_2S_2.HCl$

Calc.: C 46.8% H 5.04 %

Found: C 46.5% H 5.09%

(from 1-methyl-A and N-(*p*-toluene sulphonyl)-thiourea)

EXAMPLE 32

2-p-Aminobenzenesulphonamido-5-methyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine dihydrochloride

M.pt.: 208 — 210°C $C_{13}H_{16}N_4O_2S_2.2HCl$

Calc.: C 39.3% H 4.56%

Found: C 40.1% H 4.96%

(from 1-methyl-A and N-(*p*-aminobenzenesulphonyl)-thiourea)

EXAMPLE 33

2-[3,4-Dimethoxybenzenesulphonamido]-5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine hydrochloride

M.pt. 278 — 280°C $C_{15}H_{19}N_3O_4S_2.HCl$

Calc.: C 44.4% H 4.95%

Found: C 43.7% H 4.92%

(from 1-methyl-A and N-(3,4-dimethoxybenzenesulphonyl)-thiourea)

EXAMPLE 34

2-p-Toluenesulphonamido-5-ethyl-4,5,6,7-tetrahydro-thiazolo[5,4,-c]pyridine hydrochloride

M.pt. 255 — 257°C $C_{15}H_{19}N_3O_2S_2.HCl$

Calc.: C 48.1% H 5.38%

Found: C 47.6% H 5.39%

(from 1-ethyl-A and N-(*p*-toluenesulphonyl)-thiourea)

EXAMPLE 35

2-*p*-Methoxybenzenesulphonamido-5-ethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride

M.pt. 250°C $C_{15}H_{19}N_3O_3S_2.HCl$

Calc.: C 46.2% H 5.16%

Found: C 46.3% H 5.40%

(from 1-ethyl-A and N-(*p*-methoxybenzenesulphonyl)-thiourea)

EXAMPLE 36

2-[2,4-Dibromobenzenesulphonamido]-5-ethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride

M.pt 257 — 258°C $C_{14}H_{15}Br_2N_3O_2S_2.HCl$

Calc.: C 32.5% H 3.10%

Found: C 32.2% H 3.18%

(from 1-ethyl-A and N-(2,4-dibromobenzenesulphonyl)-thiourea)

EXAMPLE 37

2-[2,4-Dichlorobenzenesulphonamido]-5-ethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride

M.pt. 262 — 263°C $C_{14}H_{15}Cl_2N_3O_2S_2.HCl$

Calc.: C 39.2% H 3.76%

Found: C 39.1% H 3.75%

(from 1-ethyl-A and N-(2,4-dichlorobenzenesulphonyl)-thiourea)

EXAMPLE 38

2-p-Toluenesulphonamido-5-propyl-4,5,6,7-tetrahydro-thiazolo-[5,4-c]pyridine hydrochloride

M.pt. 247 — 248°C $C_{16}H_{21}N_3O_2S_2.HCl$

Calc.: C 49.5% H 5.70%

Found: C 49.7% H 5.76%

(from 1-propyl-A and N-*p*-toluenesulphonyl-thiourea)

EXAMPLE 39

2-*p*-Chlorobenzenesulphonamido-5-propyl-4-,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride

M.pt. 246 — 247°C $C_{15}H_{18}ClN_3O_2S_2.HCl$

Calc.: C 44.2% H 4.70%

Found: C C 44.4% H 4.90%

(from 1-propyl-A and N-(*p*-chlorobenzenesulphonyl)-thiourea)

EXAMPLE 40

2-[2,4-Dichlorobenzenesulphonamido]-5-propyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride

M.pt. 250 — 252°C $C_{15}H_{17}Cl_2N_3O_2S_2.HCl$

Calc.: C 40.7% H 4.08%

Found: C 40.2% H 4.28%

(from 1-propyl-A and N-(2,4-dichlorobenzenesulphonyl)-thiourea)

EXAMPLE 41

2-*p*-Toluenesulphonamido-5-isopropyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride

M.pt. 262 — 263°C $C_{16}H_{21}N_3O_2S_2.HCl$

Calc.: C 49.5% H 5.72%

Found: C 49.5% H 5.84%

(from 1-isopropyl-A and N-(*p*-toluenesulphonyl)-thiourea)

EXAMPLE 42

2-*p*-Toluenesulphonamido-5-butyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine hydrochloride

M.pt. 230 — 232°C $C_{17}H_{23}N_3O_2S_2.HCl$

Calc.: C 50.7% H 6.02%

Found: C 50.8% H 6.22%

(from 1-butyl-A and N-(*p*-toluenesulphonyl)-thiourea)

EXAMPLE 43

2-*p*-Methoxybenzenesulphonamido-5-butyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrobromide

M.pt. 225 — 226°C $C_{17}H_{23}N_3O_3S_2HBr$

Calc.: C 44.2% H 5.26%

Found: C 44.5% H 5.44%

(from 1-butyl-A and N-(*p*-methoxybenzenesulphonyl)-thiourea)

EXAMPLE 44

2-*p*-Toluenesulphonamido-5-isobutyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride

M.pt. 242°C $C_{17}H_{23}N_3O_2S_2.HCl$

Calc.: C 50.7% H 6.02%

Found: C 50.8% H 6.12%

(from 1-isobutyl-A and N(*p*-toluenesulphonyl)-thiourea)

EXAMPLE 45

2-*p*-Toluenesulphonamido-5-allyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine hydrochloride

M.pt. 230 — 232°C $C_{16}H_{19}N_3O_2S_2.HCl$

Calc.: C 49.7% H 5.20%

Found: C 49.5% H 5.23%

(from 1-allyl-A and *p*-toluenesulphonyl thiourea)

EXAMPLE 46

2-*p*-Toluenesulphonamido-5-cyclohexyl-4,5,6-,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride

M.pt. 238 — 240°C $C_{19}H_{25}N_3O_2S_2.HCl$

Calc.: C 53.3% H 6.12%

Found: C 53.0% H 6.15%

(from 1-cyclohexyl-A and *p*-toluenesulphonyl thiourea)

EXAMPLE 47

2-*p*-Toluenesulphonamido-5-phenyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine

M.pt. 238 — 240°C $C_{19}H_{19}N_3O_2S_2$

Calc.: C 59.1% H 4.97%

Found: C 59.1% H 4.84%

(from 1-phenyl-A and N-*p*-toluenesulphonylthiourea)

EXAMPLE 48

2-*p*-Toluenesulphonamido-5-benzyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine hydrochloride

M.pt. 260 — 264°C $C_{20}H_{21}N_3O_2S_2.HCl$

Calc.: C 55.0% H 5.08%

Found: C 54.8% H 4.90%

(from 1-benzyl-A and N-*p*-toluenesulphonylthiourea)

EXAMPLE 49

2-*p*-Toluenesulphonamido-5-phenylethyl-4,5,6,-7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride

M.pt. 246 — 248°C $C_{21}H_{23}N_3O_2S_2.HCl$

Calc.: C 56.0% H 5.38%

Found: C 55.8% H 5.29%

(from 1-phenylethyl-A and N-(*p*-toluene sulphonyl)-thiourea)

EXAMPLE 50

2-*p*-Methoxybenzenesulphonamido-5-phenylethyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine hydrochloride

M.pt. 238 — 240°C $C_{21}H_{23}N_3O_3S_2.HCl$

Calc.: C 54.0% H 5.18%

Found: C 53.7% H 5.45%

(from 1-phenylethyl-A and N-(*p*-methoxybezenesulphonyl)-thiourea)

EXAMPLE 51

2-*p*-Methoxybenzenesulphonamido-5-phenylethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride

M.pt. 242 — 244°C $C_{21}H_{23}N_3O_3S_2.HCl$

Calc.: C 54.0% H 5.18%

Found: C 54.2% H 5.26%

(from 1-phenyl-ethyl-A and N-(σ-methoxybenzenesulphonyl)thiourea

EXAMPLE 52

2-*o*-Chlorobenzenesulphonamido-5-phenyl-ethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride

M.pt. 240°C $C_{20}H_{20}ClN_3O_2S_2.HCl$

Calc.: C 51.0% H 4.49%

Found: C 51.1% H 4.46%

(from 1-phenyl-ethyl-A and N-(*p*-chlorobenzenesulphonyl)-thiourea)

EXAMPLE 53

2-[2,4-Dichlorobenzenesulphonamido]-5-phenyl-ethyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine hydrochloride
M.pt. 265°C $C_{20}H_{19}Cl_2N_3O_2S_2.HCl$

Calc.: C 47.6% H 4.0%

Found: C 47.9% H 4.19%

(from 1-phenyl-ethyl-A and N-(2-dichlorobenzenesulphonyl)-thiourea)

EXAMPLE 54

2-*p*-Bromobenzenesulphonamido-5-phenyl-ethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-hydrochloride

M.pt. 235 — 236°C $C_{20}H_{20}Br\ N_3O_2S_2.HCl$

Calc.: C 46.6% H 4.12%

Found: C 46.6% H 4.12%

(from 1-phenyl-ethyl-A and N-*p*-bromobenzenesulphonylthiourea)

EXAMPLE 55

2-[2,4-Dibromobenzenesulphonamido]-5-(phenyl-ethyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine hydrochloride

M.pt. 238 — 240°C $C_{20}H_{19}Br_2N_3O_2S_2.HCl$

Calc.: C 40.5% H 3.39%

Found: C 40.9% H 3.52%

(from 1-phenyl-ethyl-A and N-(2,4-dibromobenzenesulphonylthiourea))

EXAMPLE 56

2-[2,4-Dimethybenzenesulphonamido]-5-phenylethyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine hydrochloride

M.pt. 248°C $C_{22}H_{25}N_3O_4S_2.HCl$

Calc.: C 53.2% H 5.28%

Found: C 53.0% H 5.45%

(from 1-phenylethyl-A and N-(3,4-dimethoxybenzenesulphonyl)thiourea)

EXAMPLE 57

2-*p*-Toluenesulphonamido-5-benzoyl-4,5,6,7-tetrahydro-thiazolo[5,4,4-c]pyridine hydrochloride

M.pt. 98 — 100°C $C_{20}H_{19}N_3O_3S_2.HCl$

Calc.: C 53.5% H 4.48%

Found: C 53.9% H 4.76%

(from 1-benzoyl-A and N-(*p*-toluenesulphonyl)-thiourea)

EXAMPLE 58

2-Guanidino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine

M.pt. 210 — 211°C $C_{10}H_{17}N_5S$

Calc.: C 50.2% H 7.16%

Found: C 50.5% H 7.18%

(from 1-propyl-A and thiocarbamoylguanidine

EXAMPLE 59

2-*p*-Aminobenzenesulphonamido-5-(phenyl-ethyl)-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride

M.pt. = 224 — 262°C $C_{20}H_{22}N_4O_2S_2.HCl$

Calc.: C 53.2% H 5.14%

Found: C 53.4% H 5.37%

(from 1-phenyl-ethyl-A and N-(*p*-aminobenzenesulphonyl)-thiourea)

EXAMPLE 60

2-Amino-5-tert.butyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dihydrochloride

M.pt. = 223 — 225°C $C_{10}H_{17}N_3S.2HCl$

Calc.: C 42.3% H 6.75%

Found: C 42.3% H 6.95%

(from-1-tert. butyl-A and thiourea)

EXAMPLE 61

2-Amino-5-ethyl-7-methyl-4,5,6,7-tetrahydro-thiazolo-[5,4-c]-pyridine

$C_9H_{15}N_3S$

M.pt = 98 — 100°C

Calc.:	C 54.8%	H 7.67%
Found:	C 54.5%	H 7.72%

(from 1-ethyl-5-methyl-A and thiourea)

EXAMPLE 62

2-Amino-5-acetyl-4,5,6,7-tetrahydro-thiazolo-[5,4-c]pyridine-hydrochloride

$C_8H_{11}N_3OS$

M.pt. = 106°C

Calc.:	C 41.10%	H 5.17%
Found:	C 40.70%	H 5.38%

(from 1-acetyl-A and thiourea)

EXAMPLE 63

2-Amino-5[2-phenoxyethyl]-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dihydrochloride

$C_{14}H_{17}N_3SO \cdot 2HCl$

M.pt. = 228 — 229°C

Calc.:	C 48.2%	H 5.5%
Found:	C 48.2%	H 5.4%

(from 1[2-phenoxy-ethyl]-A and thiourea)

EXAMPLE 64

2-Amino-5-[2-*p*-chlorophenyl-ethyl]-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine

$C_{14}H_{16}ClN_3S$

M.pt. = 191 — 192°C

Calc.:	C 57.2%	H 5.5%
Found:	C 57.4%	H 5.5%

(from 1[2-*p*-chlorophenyl-ethyl]-A and thiourea)

EXAMPLE 65

2-Amino-5-*p*-toluenesulphonyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]-pyridine

$C_{13}H_{15}N_3O_2S$

M.pt = 182 — 183°C.

Calc.:	C 50.5%	H 4.90%
Found:	C 50.5%	H 5.16%

(from 1-*p*-toluenesulphonyl-A and thiourea)

EXAMPLE 66

2-Amino-5-cyclopropylcarbonyl-4,5,6,7-tetrahydro-thiazolo-[5,4-c]pyridine

M.pt. = 163 — 165°C. $C_{10}H_{13}N_3OS$

Calc.: C 54.2% H 5.82%

Found: C 54.3% H 5.53%

(from 1-cyclopropylcarbonyl-A and thiourea)

EXAMPLE 67

2-Cyclopropylcarbamido-5-cyclopropylcarbonyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine

M.pt. = 210°C $C_{14}H_{17}N_3O_2S$

Calc.: C 57.6% H 5.89%

Found: C 57.3% H 6.10%

(from 2-amino-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine and cyclopropylcarboxylic acid chloride)

EXAMPLE 68

2-Acetamido-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]-pyridine hydrochloride

M.pt. 305 — 306°C $C_{11}H_{17}N_3OS \cdot HCl$

Calc.: C 48.0% H 6.59%

Found: C 48.2% H 6.62%

(from 2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]-pyridine and acetic anhydride)

EXAMPLE 69

2-(p-Chlorobenzamido)-5-propyl-4,5,6,7-tetrahydro-thiazolo-[5,4-c]pyridine hydrochloride

M.pt. = 275 — 277°C. $C_{16}H_{18}ClN_3OS \cdot HCl$

Calc.: C 51.60% H 5.14%

Found: C 51.90% H 5.31%

(from 2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine and *p*-chlorobenzoyl chloride in pyridine)

EXAMPLE 70

2-Methylamino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dihydrochloride

M.pt. = 220 — 221°C $C_{10}H_{17}N_3S \cdot 2HCl$

Calc.: C 42.2% H 6.72%

Found: C 41.65% H 7.08%

(from 1-propyl-A and N-methylthiourea)

EXAMPLE 71

2-Ethylamino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dihydrochloride

M.pt. = 228 — 229°C $C_{11}H_{19}N_3S$. 2HCl

Calc.: C 44.3% H 7.09%

Found: C 44.4% H 6.95%

(from 1-propyl-A and N-ethyl-thiourea)

EXAMPLE 72

2-Propylamino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dihydrochloride

M.pt. = 231 — 232°C $C_{12}H_{21}N_3S$

Calc.: 46.2% H 7.52%

Found: C 45.7% H 7.30%

(from 1-propyl-A and N-propyl-thiourea)

EXAMPLE 73

2-Allylamino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dihydrochloride

M.pt. = 224 — 225°C $C_{12}H_{19}N_3S$. 2HCl

Calc.: C 46.5% H 8.81%

Found: C 46.2% H 8.79%

(from 1-propyl-A and N-allyl-thiourea)

EXAMPLE 74

2-Cyclohexylamino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dihydrochloride

M.pt. = 230 — 232°C $C_{15}H_{25}N_3S$. 2HCl

Calc.: C 51.2% H 7.72%

Found: C 51.1% H 7.64%

(from 1-propyl-A and N-cyclohexyl-thiourea)

EXAMPLE 75

2-Anilino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dihydrochloride

M.pt. = 224 — 226°C $C_{15}H_{19}N_3S$. 2HCl

Calc.: C 52.0% H 6.1%

Found: C 51.9% H 6.0%

(from 1-propyl-A and N-phenyl-thiourea)

EXAMPLE 76

2-[2-Phenylethylamino]-5-propyl-4,5,6,7-tertahydro-thiazolo[5,4-c]pyridine dihydrochloride

M.pt. = 237 — 238°C. $C_{17}H_{23}N_3S \cdot 2HCl$

Calc.: C 54.6% H 6.73%

Found: C 54.8% H 6.95%

(from 1-propyl-A and N[2-phenyl-ethyl]-thiourea)

EXAMPLE 77

2-Morpholino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dihydrochloride

M.pt. = 227 — 233°C $C_{13}H_{21}N_3OS \cdot 2HCl$

Calc.: C 45.9% H 6.8%

Found: C 45.7% H 6.8%

(from 1-propyl-A and thiocarbamoylmorpholine)

EXAMPLE 78

2-*p*-Bromobenzenesulphonamido-4,5,6,7-tetrahydro-thiazolo-[pyridine hydrochloride

M.pt. = 262°C $C_{12}H_{12}BrN_3O_2S_2 \cdot HCl$

Calc.: C 35.0% H 3.19%

Found: C 35.2% H 3.25%

(from 1-acetyl-A and N-[*p*-bromobenzenesulphonyl]-thiourea in pyridine and hydrolysis of the resulting 2-(*p*-bromobenzenesulphonamido)-5-acetyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine in an acid medium).

EXAMPLE 79

2-*p*-Bromobenzene sulphonamido-5-ethyl-4,5,6,7-tetrahydrothiazolo-[5,4-c]pyridine hydrochloride

M.pt. = 250°C $C_{14}H_{16}BrN_3O_2S_2 \cdot HCl$

Calc.: C 38.45% H 3.90%

Found: C 37.9% H 4.07%

(from 1-ethyl-A and N-[*p*-bromobenzenesulphonyl]-thiouresa in pyridine])

EXAMPLE 80

2-[*p*-Methylthio-benzenesulphonamido]-5-ethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride

M.pt. = 240 — 242°C $C_{15}H_{19}N_3O_2S_3 \cdot HCl\ H_2O$

Calc.: C 42.50% H 5.23%

Found: C 42.90% H 5.14%

(from 1-ethyl-A and N-[*p*-methylthio-benzenesulphonyl]-thiourea in pyridine)

EXAMPLE 81

2-[*m*-Methylsulphonyl-benzenesulphonamido]-5-ethyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine hydrochloride
M.pt. = 150 — 151°C $C_{15}H_{19}N_3O_4S_3$. HCl

Calc.: C 41.4% H 4.60%

Found: C 41.7% H 4.75%

(from 1-ethyl-A and N-[*m*-methylsulphonyl-benzenesulphonyl]thiourea in pyridine

EXAMPLE 82

2-[*m*-Methylsulphonyl-benzenesulphonamido]-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine hydrochloride

M.pt. = 197°C $C_{16}H_{21}N_3O_4S_3$. HCl

Calc.: C 42.5% H 4.91%

Found: C 42.7% H 5.05%

(from 1-propyl-A and N-[*m*-methylsulphonyl-benzenesulphonyl]-thio-urea in pyridine)

EXAMPLE 83

2-*p*-Bromobenzenesulphonamido-5-cyclohexyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine hydrochloride
M.pt = 252°C $C_{18}H_{22}BrN_3O_2S_2$. HCl

Calc.: C 43.8% H 4.68%

Found: C 43.9% H 4.86%

(from 1-cyclohexyl-A and N[*p*-bromobenzenesulphonyl]-thiourea in pyridine)

EXAMPLE 84

2-[*m*-Methylsulphonyl-benzenesulphinamido]-5-cyclohexyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine hydrochloride

M.pt. = 248°C $C_{19}H_{25}N_3O_4S_3$. HCl

Calc.: C 46.3% H 5.32%

Found: C 45.9% H 5.34%

(from 1-cyclohexyl-A and N[*m*-methylsulphonyl-benzenesulphonyl]-thiourea in pyridine)

EXAMPLE 85

2[*m*-Methylsulphonyl-benzenesulphonamido]-5-benzyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine hydrochloride

M.pt. = 244°C $C_{20}H_{21}N_3O_4S_3$. HCl

Calc.: C 48.0% H 4.43%

Found: C 47.8% H 4.48%

(from 1-benzyl-A and N[*m*-methylsulphonyl-benzenesulphonyl]thiourea)

EXAMPLE 86

2-[*p*-Methylsulphonyl-benzenesulphonamido]-5-phenylethyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine hydrochloride

M.pt. = 225°C $C_{21}H_{23}N_3O_4S_3 \cdot HCl$

Calc.: C 49.1% H 4.70%

Found: C 4.90 % H 4.85%

(from 1-phenylethyl-A and *p*-methylsulphonyl-benzenesulphonylthiourea in pyridine)

EXAMPLE 87

2-[*m*-Methylsulphonyl-benzenesulphonamido]-5-phenylethyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine hydrochloride

M.pt. = 210 — 212°C $C_{21}H_{23}N_3O_4S_3 \cdot HCl$

Calc.: C 49.1% H 4.71%

Found: C 48.7% H 4.79%

(from 1-phenyl-ethyl-A and *m*-methylsulphonyl benzenesulphonylthiourea in pyridine)

EXAMPLE 88

2-[*p*-Toluenesulphonamido]-5-p-chlorophenyl-ethyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine hydrochloride hydrate

M.pt. = 230 — 231°C $C_{21}H_{22}ClN_3O_2S_2.HCl.H_2O$

Calc.: C 50.2 % H 5.02%

Found: C 50.7% H 4.94%

(from 1-*p*-chlorophenylethyl-A and *p*-toluenesulphonyl-thiourea in pyridine)

EXAMPLE 89

2-[3,4-Dimethoxybenzenesulphonamido]-5-(*p*-chlorophenyl-ethyl]-4,5,6,7-tetrahydro-thiazolo-[5,4-c]pyridine hydrochloride hydrate

M.pt. = 233.5°C $C_{22}H_{24}ClN_3O_4S_2 \cdot HCl \cdot H_2O$

Calc.: C 48.2% H 4.96%

Found: C 48.0% H 4.85%

(from 1-*p*-chlorophenylethyl-A and 3,4-dimethyloxybenzenesulphonylthiourea)

Example 90

2-[*m*-Methylsulphonyl-benzenesulphonamido]-5-(*p*-chlorophenyl-ethyl)-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine hydrochloride

M.pt. = 251 — 252°C $C_{21}H_{22}ClN_3O_4S_3 \cdot HCl$

Calc.: C 46.0% H 4.22%

Found: C 46.2% H 4.29%

(from 1-*p*-chlorophenylethyl-A and *m*-methylsulphonyl-benzene sulphonyl-thiourea in pyridine)

EXAMPLE 91

2-[*p*-Bromobenzenesulphonamido]-5[3,4-dimethoxy-phenyl-ethyl]-4,5,6,7-tetrahydro-thiazolo-[5,4-c]pyridine hydrochloride

M.pt. = 238 — 240°C $C_{22}H_{24}BrN_3S_2O_4 \cdot HCl$

Calc.: C 45.8% H 4.38%

Found: C 45.2% H 4.52%

(from 1-(β-[3,4-dimethoxyphenyl]-ethyl)-A and *p*-bromobenzencsulphonylthiourea in pyridine)

EXAMPLE 92

2-[*p*-Toluencsulphonamido]-5[3,4-dimethoxy-phenyl-ethyl]-4,5,6,7-tetrahydro-thiazolo[5,4-c]-pyridine hydrochloride

M.pt. — 252°C $C_{23}H_{27}N_3O_4S_2 \cdot HCl$

Calc.: C 54.1 % H 5.53 %

Found: C 53.7 % H 5.60%

(from 1-(β-[3,4-dimethoxy-phenyl]-ethy')-A and *p*-toluenesulphonylthiourea in pyridine)

EXAMPLE 93

2-[*p*-Toluenesulphonamido]-5-[α-phenylethyl]-4,5,6,7-tetrahydrothiazolo[5,4-c)] hydrochloride hemidhydrate

M.pt. = 238°C $C_{21}H_{23}N_3O_2S_2 \cdot HCl \cdot 1/2\ H_2O$

Calc.: C 54.9% H 5.49%

Found: C 54.9% H 5.49%

(from α-phenylethyl-A and *p*-toluenesulphonyl-thiourea in pyridine)

Example 94

2-[*p*-Bromobenzenesulphonamido]-5-[α-phenyl-ethyl]-4,5,6,7-tetrahydro-thiazolo[5,4-c]-> pyridine hydrochloride

M.pt. = 238°C $C_{20}H_{20}BrN_3O_2S_2 \cdot HCl$

Calc.: C 46.7% H 4.10%

Found: C 46.4% H 4.17%

(from α-phenylethyl-A and *p*-bromobenzenesulphonyl-thiourea in pyridine)

EXAMPLE 95

2-[*m*-Methylsulphonyl-benzenesulphonamido]-5-α-[phenyl-ethyl]-4,5,6,7-tetrahydro-thiazole [5,4-c]pyridine hydrochloride

M.pt = 236 — 237°C $C_{21}H_{23}N_3S_4O_3 \cdot HCl$

Calc.: C 49.1% H 4.71%

Found: C 49.2% H 4.78%

(from 1α-phenyl-ethyl-A and *m*-methylsulphonyl-benzenesulphonylthiourea in pyridine)

EXAMPLE 96

2-[*p*-Methoxybenzenesulphonamido]-5-[α-phenylethyl]4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine hydrochloride hemihydrate

M.pt. = 230°C $C_{21}H_{23}N_3O_3S_2$. HCl . 1/2 H_2O

Calc.: C 53.0% H 5.31%

Found: C 52.9% H 5.35%

(from α-phenyl-ethyl-A and *p*-methoxybenzenesyulphonyl-thiourea in pyridine)

EXAMPLE 97

2-Tetramethlenimino-5-propyl-4,5,6,7-tetrahydro-thiazolo-[5,4-c]pyridine dihydrochloride

M.pt. = 225°C $C_{13}H_{21}N_3S$. 2 HCl

Calc.: C 48.1% H 7.15%

Found: C 48.1% H 7.17%

(from 1-propyl-A and N,N-tetramethylenethiourea)

EXAMPLE 98

2-Hexamethylenimino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dihydrochloride

M.pt. = 208°C $C_{15}H_{25}N_3S$. 2 HCl

Calc.: C 51.2% H 7.73%

Found: C 51.3% H 7.82%

(from 1-propyl-A and N,N-hexamethyleniminothiourea)

EXAMPLE 99

2[4-Methylpiperazin-1-yl]-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine trihydrochloride

M.pt. = 224°C $C_{14}H_{24}N_4S$. 3 HCl

Calc.: C 43.1 % H 6.98%

Found: C 42.7% H 7.35%

(from 1-propyl-A and 1-thiocarbamoyl-4-methyl-piperazine)

EXAMPLE 100

2-Diethylamino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dihydrochloride

M.pt. = 188 — 190°C $C_{13}H_{23}N_3S$. 2 HCl

Calc.: C 47.9 % H 7.73%

Found: C 47.5% H 8.06%

(from 1-propyl-A and N,N-diethylthiourea)

EXAMPLE 101

2-[N-methyl-cyclohexylamino]- propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine hydrochloride

M.pt. = 224°C $C_{16}H_{27}N_3S \cdot HCl$

Calc.: C 58.1% H 8.55%

Found: C 57.7% H 8.41%

(from 1-propyl-A and N-cyclohexyl-N-methyl-thiourea)

EXAMPLE 102

2-Diallylamino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine

M.pt. = 20°C $C_{15}H_{33}N_3S$

Calc.: C 64.9% H 8.35%

Found: C 64.4% H 8.46%

(from 1-propyl-A and N,N-diallylthiourea)

EXAMPLE 103

2-Amino-5[2-methoxy-ethyl]-4,5,6,7-tetrahydro-thiazolo[5,4,-c]pyridine dihydrochloride

M.pt. = 205° $C_9H_{15}N_3OS \cdot 2\ HCl$

Calc.: C 37.8% H 5.98%

Found: C 37.7% H 6.14%

(from 1-[2-methoxy-ethyl]-A and thiourea)

Examples of pharmaceutical compositions containing 2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridinedihydrochloride (all temperatures in °C.)

A) Formulations for administration to adults

1.) Dragees containing 5 mg. of 2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo-[5,4-c]pyridine dihydrochloride

Composition:
1 Dragee core contains:

2-Amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-dihydrochloride	5.0 mg
Lactose	33.5 mg
Corn starch	10.0 mg
Gelatine	1.0 mg
Magnesium stearate	0.5 mg
	50.0 mg

Method of preparation:

The mixture of active compound with lactose and corn starch is granulated with a 10% aqueous gelatine solution through a 1 mm sieve, dried at 40° and again rubbed through the said sieve. The granulate thereby obtained is mixed with magnesium stearate and compressed to form the dragee cores. This preparation must be carried out in the dark.

Weight of core: 50 mg

Die: 5 mm, convcave

The dragee cores thus obtained are coated by known processes with a coating consisting substantially of Sugar and talcum. The finished pills are polished with beeswax.

Weight of pill: 100 mg

2.) Drop solution containing 5 mg. of 2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo-[5,4-c]pyridine dihydrochloride per 1 ml

Composition:

100 ml of the solution for the drops contain:

Methyl *p*-hydroxybenzoate		0.035 g.
Propyl *p*-hydroxybenzoate		0.015 g.
Aniseed oil		0.05 g
Menthol		0.06 g
Pure ethanol		10.0 g
2-Amino-5-propyl-4,5,6,7-tetrahydro-thiazolo [5,4-c]pyridine dihydrochloride		0.5 g
Citric acid		0.7 g
Secondary sodium phosphate . 2 H_2O		0.3 g
Sodium cyclamate		1.0 g
Glycerol		15.0 g
Distilled water	up to	100.0 ml

Method of preparation:

The *p*-hydroxybenzoic acid esters, aniseed oil and menthol are dissolved in ethanol (Solution A). The buffer substances, active substance and sodium cyclamate are dissolved in distilled water and glycerol is added (Solution B).

Solution A is then stirred into solution B and the mixture is made up to the given volume with distilled water. The combined solution for the drops is filtered through a suitable filter. Preparation and filling up of the drop solution must be carried out under protection against light in a protective gas atmosphere.

1 ml of drop solution contains 5 mg of 2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo [5,4-c]pyridine dihydrochloride

3.) Suppositories with 10 mg of 2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo [5,4-c]pyridine-dihydrochloride

1 suppository contains:

2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-dihydrochloride	10.0 mg
Suppository base (e.g. Witepsol W 45 registered Trade Mark)	1690.0 mg
	1700.0 mg

Method of preparation:

The finely powdered substance is stirred with the aid of an immersion homogeniser into the molten suppository base which has been cooled to 40°C. At 35°, the composition is poured out into slightly pre-cooled moulds.

Weight of suppository: 1.7 g.

4.) Ampoules with 5 mg of 2-amino-5-propyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine dihydrochloride

1 ampoule contains:

2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]-pyridine dihydrochloride		5.0 mg
Citric acid		7.0 mg
Secondary sodium phosphate . $2H_2O$		3.0 mg
Sodium pyrosulphite		1.0 mg
Distilled water	up to	1.0 ml

Method of preparation:

The buffer substances, active substance and sodium pyrosulphite are successively dissolved in water which has been boiled and then cooled and simultaneously gasified with CO_2. The solution is made up to the given volume with the treated water and filtered free from pyrogenic impurities.

The product is filled into brown ampoules under an atmosphere of a protective gas.

Sterilisation time: 20 minutes at 120°.

The process of preparation and filling of the ampoules must be carried out in the dark.

B.) Formulations for administration to children

1.) Dragees with 1 mg. of 2-amino-5-propyl-4,5,6,7-tetrahydro-Thiazolo[5,4-c] pyridine-dihydrochloride

1 dragee core contains:

2-Amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine dihydrochloride	1.0 mg
Lactose	35.5 g
Corn starch	12.0 mg
Gelatine	1.0 mg
Magnesium stearate	0.5 mg
	50.0 mg

Method of preparation:

Analogous to A/1.

Weight of dragee core:	50 mg
Die:	5 mm, curved
Weight of dragee:	100 mg

2.) Syrup with 1 mg of 2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dihydrochloride per 5 ml.

Composition

100 ml of syrup contain:

2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dihydrochloride		0.02 g
Sugar		70.0 g
Citric acid		0.7 g
Secondary sodium phosphate . $2H_2O$		0.3 g
Methyl *p*-hydroxybenzoate		0.07 g
Propyl *p*-hydroxybenzoate		0.03 g
Edible red colouring		0.007 g
Edible yellow colouring		0.023 g
Natural raspberry flavouring		0.6 g
Pure ethanol		2.0 g
Distilled water	up to	100.0 ml.

Method of Preparation

Distilled water is heated to 80° and the *p*-hydroxybenzoic acid esters, buffer substances, active substance, colouring matter and sugar are successively dissolved therein. The raspberry flavouring and ethanol are then added and the solution is made up to the given volume. The preparation and filling up of the syrup must be carried out under protection against light and in a protective gas atmosphere.

5 ml of Syrup solution contain 1 mg. of 2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo [5,4-c]pyridine dihydrochloride

3.) Suppositories with 2 mg of 2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo-[5,4-c]pyridine dihydrochloride

1 suppository contains:

2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo [5,4-c]pyridine dihydrochloride	2.0 mg
suppository base (e.g. Witepsol W 45)	998.0 mg
	1000.0 mg

Method of preparation:

Analogous to A/3

Weight of suppository: 1.0 g

C) Formulations for administration to babies

1.) Syrup with 0.5 mg of 2-amino-5-propyl-4,5,6,7-tetrahydrothiazolo[5,4-c] pyridine dihydrochloride per 5 ml

Composition:

100 ml of syrup contain:

2-Amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-dihydrochloride	0.01 g
Sugar	70.0 g
Citric acid	0.7 g
Secondary sodium phosphate $2H_2O$	0.3 g
Methyl *p*-hydroxybenzoate	0.07 g
Propyl *p*-hydroxybenzoate	0.03 g
Edible red colouring	0.007 g
Edible yellow colouring	0.023 g
Natural raspberry flavouring	0.6 g
Pure ethanol	2.0 g
Distilled water	up to 100.0 ml

Method of preparation:

Analogous to B/2

5-ml of the syrup contains 0.5 mg of 2-amino-5-propyl-4,5,6,7-tetrahydrothiazolo[5,4-c] pyridine dihydrochloride

2.) Suppositories with 1 mg of 2-amino-5-propyl-4,5,6,7-tetra-hydro-thiazolo [5,4-c]pyridine dihydrochloride

1 suppository contains:

2-Amino-5-propyl-4,5,6,7-tetrahydro-thiazolo [5,4-c]pyridine-dihydrochloride	1.0 mg
Suppository base (e.g. Witepsol W 45)	999.0 mg
	1000.0 mg

Method of preparation:

Analogous to A/3

Weight of suppository: 1.0 g

D) Combinations of preparations

1.) Suppositories with 10 mg 2-amino-5-propyl-4,5,6,7-tetrahydrothiazolo[5,4-c] pyridine-dihydrochloride and 200 mg butazolidine

1 suppository contains:

2-Amino-5-propyl-4,5,6,7-tetrahydro-thiazolo-[5,4-c] pyridine-dihydrochloride	10.0 mg
Butazolidine	200.0 mg
Suppository base (e.g. Witepsol W 45)	1510.0 mg
	1720.0 mg

Method of preparation:

Analogous to A/3

Weight of suppository: 1.72 g

2.) Syrup with 5 mg 2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridine dihydrochloride, 40 mg 1-(*p*-chlorophenyl)-2,3-dimethyl-4-dimethylamino-butanol-(2)-hydrochloride and 5 mg codein phosphate per 10 ml

Composition:

100 ml of syrup contain:

2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine dihydrochloride	0.05 g
1-(p-chlorophenyl)-2,3-dimethyl-4-dimethylamino-butanol-(2)-hydrochloride	0.04 g
Codein phosphate	0.05 g
Sugar	65.0 g
Citric acid	0.7 g
Secondary sodium phosphate . 2 H_2O	0.3 g
Sodium benzoate	0.2 g
Ammonium chloride	0.7 g
Edible red colouring	0.007 g
Edible yellow colouring	0.023 g
Natural raspberry flavouring	0.6 g
Pure ethanol	2.0 g
Distilled water	up to 100.0 ml

Method of preparation:

40 ml of water are heated to 80° and the sugar dissolved therein. The syrup is cooled and strained. The buffer substances, sodium benzoate, ammonium chloride, colouring matter and active substances are dissolved in the remainder of the water and mixed with the syrup. Finally, the raspberry flavouring and ethanol are added and the syrup filtered through a suitable filter. Preparation and filling of the syrup into containers must be carried out under protection against light and in a protective gas atmosphere.

10 ml of syrup contain 5 mg of 2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]-pyridine-dihydrochloride, 40 mg 1-(p-chlorophenyl)-2,3-dimethyl-4-dimethylamino-butanol-(2)-hydrochloride and 5 mg of codein phosphate

3.) Dragees with 5 mg of 2-amino-5-propyl-4,5,6,7-tetrahydrothiazolo[5,4-c]-pyridine dihydrochloride, 25 mg 2,6-bis-(di-ethanolamino)-4,8-dipiperidino-pyrimido[5,4,-d]pyrimidine and 0.25 mg digoxine

1 dragee core contains:

2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine dihydrochloride	5.0 mg
2,6-bis-(diethanolamine)-4,8-dipiperidinopyrimido [5,4-d]pyridimidine	25.0 mg
Digoxine	0.25 mg
Lactose	61.75 mg
Potato starch	25.0 mg
Polyvinyl pyrrolidone	2.0 mg
Magnesium stearate	1.0 mg
	120.0 mg

Method of preparation:

The active substances, lactose and potato starch, having all been intensively mixed together, are granulated with a 10% solution of polyvinyl pyrrolidone in ethanol through a 1.5 mm sieve, dried at 40° and again rubbed through a 1 mm sieve. The granulate thereby obtained is mixed with magnesium stearate and compressed to form the dragee cores.

Weight of dragee core: 120 mg

Die: 7 mm, curved

The dragee cores prepared in this way are coated by a known process with a coating consisting substantially of sugar and talcum. The finished pills are polished with beeswax.

Weight of pill: 200 mg

4.) Gelatine capsules with 5 mg of 2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo [5,4-c]pyridine dihydrochloride and 10 mg codein phosphate

1 capsule contains:

2-Amino-5-propyl-4,5,6,7-tetrahydro-thiazolo [5,4-c]pyridine dihydrochloride	5.0 mg
Codein phosphate	10.0 mg
Tartaric acid	1.0 mg
Corn starch	84.0 mg
	100.0 mg

Method of preparation:

The substances are intensively mixed together and filled into opaque capsules of suitable size.

Capsule filling: 100 mg

5.) Ampoules with 5 mg 2-amino-5-propyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine-dihydrochloride and 100 mg dolantin

1 ampoule contains:		
2-amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine dihydrochloride		5.0 mg
dolantin (registered Trade Mark)		100.0 mg
citric acid		10.5 mg
secondary sodium phosphate . 2 H_2O		4.5 mg
sodium pyrosulphite		1.0 gm
distilled water	up to	2.0 ml

Method of preparation:

Analogous to A/4

Filling: into brown ampoules under a protective gas atmosphere

Sterilisation time: 20 minutes at 120°.

6.) Depot dragees with 15 mg 2-amino-5-propyl-4,5,6,7-tetrahydrothiazolo[5,4-c] pyridine-dihydrochloride

Composition:

1 dragee core contains:	
2-Amino-5-propyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridine-dihydrochloride	10.0 mg
carboxymethylcellulose	35.0 mg
polyvinyl acetate	4.8 mg
magnesium stearate	0.2 mg
	50.0 mg
2-Amino-5-propyl-4,5,6,7-tetrahydro-thiazolo [5,4-c]pyridine-dihydrochloride in the dragee coating	5.0 mg

Method of preparation:

The active substance and carboxymethylcellulose are mixed together and granulated with a 25% solution of polyvinyl acetate in acetone through a 1 mm sieve. After it has been dried at 40°, the granulate is again passed through the above sieve and mixed with magnesium stearate. The mixture is compressed to form the dragee cores.

Weight of the dragee core: 50 mg

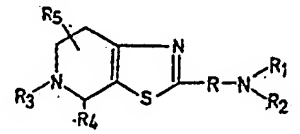
Die: 5 mm, curved

The dragee cores prepared in this way are coated by a known process with a coating consisting substantially of sugar and talcum. At the start of this process, the active substance in the form of a powder at a concentration of 66% together with talcum is added to the moist pill centres rotating in the tank in a quantity corresponding to 5 mg of 2-amino-5-propyl-4,5,6,7-tetrahydrothiazolo[5,4-c]pyridine dihydrochloride per dragee. The dragees are polished with beeswax.

Weight of dragee: 100 mg.

WHAT WE CLAIM IS:—

1. Compounds of the general formula

I 

[in which R_1 represents a hydrogen atom, an alkyl radical having 1—6 carbon atoms, an alkenyl radical having 2—6 carbon atoms which may be substituted with halogen, a cycloalkyl radical having 3—8 carbon atoms, an aryl radical having 6—10 carbon atoms, an aralkyl radical having 7—9 carbon atoms, an acyl radical derived from an aliphatic or aromatic carboxylic acid or sulphonic acid, a carbamoyl radical or an amidino radical;

R_2 represents a hydrogen atom, an alkyl radical having 1—6 carbon atoms, an alkenyl radical which has 2—6 carbon atoms and may be substituted with a halogen atom, a cycloalkyl radical or, together with the nitrogen atom and R_1, forms a heterocyclic ring which may be interrupted by a further hetero atom and/or substituted by a hydroxyl group, a methyl or a phenyl group;

R_3 represents a hydrogen atom, an alkyl radical having 1—6 carbon atoms, an alkenyl radical having 2—6 carbon atoms which may be substituted with a halogen atom, a cycloalkyl radical having 3—8 carbon atoms, an aryl radical having 6—10 carbon atoms or an aralkyl radical having 7—9 carbon atoms, an acyl radical derived from an aliphatic or aromatic carboxylic acid or sulphonic acid, or a carbamoyl, thiocarbamoyl or amidino radical; and, where at least one of the groups R_1, R_2 and R_3 represents an alkyl group, said group may be substituted by a hydroxyl, alkoxy, aryloxy or cycloalkyl group, or a carboxyl, carbalkoxy or an amido radical; and, where at least one of the groups R_1, R_2 and R_3 represents an aromatic group, said group may be substituted by halogen atoms, hydroxyl, alkyl, alkoxy, alkylthio, alkylsulphonyl, alkylene dioxy, amino, alkylamino, acylamino or aminosulphonyl groups;

R_4 and R_5, which may be the same or different, represent hydrogen atoms, alkyl groups with 1 to 3 carbon atoms, aryl or aralkyl radicals, and R represents a carbon-nitrogen bond or a divalent aliphatic hydrocarbon radical having 1 to 3 carbon atoms] and their physiologically acceptable salts of inorganic and organic acids.

2. Compounds as claimed in claim 1 in which R_1 and R_2 both represent hydrogen atoms and R is a carbon-nitrogen bond.

3. Compounds as claimed in claim 1 in which at least one of the groups R_1 and R_2 represents an alkyl group and R is a carbon-nitrogen bond.

4. Compounds as claimed in claim 1 which at least one of the groups R_1 and R_2 represents an alkenyl group and R is a carbon-nitrogen bond.

5. Compounds as claimed in claim 4 in which at least one of the groups R_1 and R_2 represents an allyl group.

6. Compounds as claimed in claim 1 in which R_1 or R_2 represents an acyl group derived from a sulphonic acid and A is a carbon-nitrogen bond.

7. Compounds as claimed in claim 6 in which the acyl group is a free or substituted benzenesulphonyl group.

8. Compounds as claimed in claim 6 in which the acyl group is a free or substituted toluenesulphonyl group.

9. Compounds as claimed in any of the preceding claims in which R_3 represents an alkyl group.

10. Compounds as claimed in claim 9 in which R_3 represents an alkyl group containing 1 to 3 carbon atoms.

11. Compounds as claimed in any of claims 1 to 8 in which R_3 represents a phenyl-ethyl group.

12. 2 - Amino - 4,5,6,7 - tetrahydro - thiazolo[5,4-c]pyridine.

13. 2 - Amino - 5 - methyl - 4,5,6,7 - tetrahydro - thiazolo[5,4-c]pyridine.

14. 2 - Amino - 5 - ethyl - 4,5,6,7 - tetrahydro - thiazolo[5,4-c]pyridine.

15. 2 - Amino - 5 - propyl - 4,5,6,7 - tetrahydro - thiazolo[5,4-c]pyridine.

16. 2 - *p* - Toluenesulphonamido - 5 - ethyl - 4,5,6,7 - tetrahydro - thiazolo[5,4-c]-pyridine.

17. 2 - [2,4 - dibromobenzenesulphonamido] - 5 - ethyl - 4,5,6,7 - tetrahydro - thiazolo[5,4-c]pyridine.

18. 2 - *p* - Toluenesulphonamido - 5 - (phenyl - ethyl) - 4,5,6,7 - tetrahydrothiazolo-[5,4-c]pyridine.

19. 2 - *p* - Methoxybenzenesulphonamido-5 - (phenyl - ethyl) - 4,5,6,7 - tetrahydrothiazolo[5,4-c]pyridine.

20. 2 - *p* - Bromobenzenesulphonamido-5-(phenyl - ethyl) - 4,5,6,7 - tetrahydro - thiazolo[5,4-c]pyridine.

21. 2 - [2,4 - Dibromobenzenesulphonamido] - 5 - (phenyl - ethyl) - 4,5,6,7 - tetrahydro - thiazolo[5,4-c]pyridine.

22. 2 - [3,4 - Dimethoxybenzenesulphonamido] - 5 - (phenyl - ethyl) - 4,5,6,7 - tetrahydro - thiazolo[5,4-c]pyridine.

23. 2 - Ethylamino - 5 - propyl - 4,5,6,7-tetrahydro - thiazolo[5,4-c]pyridine.

24. 2 - Propylamino - 5 - propyl - 4,5,6,7-tetrahydro - thiazolo[5,4-c]pyridine.

25. 2 - Allylamino - 5 - propyl - 4,5,6,7-tetrahydro - thiazolo[5,4-c]pyridine.

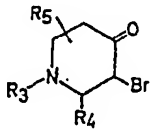
26. Compounds as claimed in any of the preceding claims in the form of their physiologically acceptable mono- or di- or tri- acid

addition salts with hydrochloric, hydrobromic, sulphuric, phosphoric, succinic, tartaric, citric, adipic, maleic, or fumaric acids.

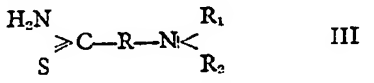
27. Compounds as claimed in any of claims 12 to 25 in the form of their mono- or dihydrochlorides.

28. Compounds as claimed in claim 1, other than as claimed in any of claims 12 to 25, as herein described.

29. A process for the preparation of compounds of general formula I (as defined in claim 1) which comprises reacting a hydrohalic acid salt of a 3 - bromo - piperidone - (4) of the formula

II 

(in which R_3, R_4 and R_5 are as defined in claim 1) with a substituted thiourea or thioamide of the formula

 III

(in which R_1, R_2 and R are as defined in claim 1).

30. A process as claimed in claim 29 in which the 3-bromo-piperidone-(4) is in the form of its hydrobromide.

31. A process as claimed in claim 29 or claim 30 in which the reaction is effected in the presence of an inert solvent.

32. A process as claimed in claim 31 in which the solvent is water, an aliphatic alcohol or a mixture thereof, an aromatic hydrocarbon or a tertiary organic base.

33. A process as claimed in claim 31 or claim 32 in which the reaction is effected at a temperature between ambient temperature and the boiling point of the solvent.

34. A process as claimed in any of claims 29 to 33 in which the reaction is effected in the presence of an acid binding agent.

35. A process as claimed in claim 34 in which the acid binding agent is an inorganic or tertiary organic base.

36. A process as claimed in claim 29 in which the compounds of general formula I are subsequently converted into their physiologically acceptable acid addition salts by treatment with a corresponding acid.

37. A process for the preparation of compounds of the general formula I (in which R_5 represents a hydrogen atom) which comprises reacting a corresponding compound of general formula I (in which R_5 represents an acyl group derived from aliphatic or aromatic carboxylic acid and R_1 represents a group other than said acyl group) with a saponifying agent.

38. A process for the preparation of compounds of the general formula I (as defined in claim 1 except that R_3 has a meaning other than a hydrogen atom or an aryl radical) in which a corresponding compound of formula I (in which R_6 represents a hydrogen atom) is reacted with an alkylating, alkenylating, cycloalkylating, aralkylating, acylating, carbamoylating, thiocarbamoylating or amidinating agent.

39. A process as claimed in claim 29 substantially as herein described.

40. A process as claimed in claim 29 substantially as herein described with reference to any of Examples 1—103.

41. Compounds as claimed in claim 1 whenever prepared by a process as claimed in any of claims 29 to 40.

42. Pharmaceutical compositions comprising, as active ingredient, at least one of the compounds as claimed in claim 1 in association with a pharmaceutical carrier or excipient.

43. Compositions as claimed in claim 42 in the form of dosage units.

44. Compositions as claimed in claim 43 for administration to adults, containing 0.5 to 20 mg. of active ingredient per dosage unit.

45. Compositions as claimed in claim 44 containing 1 to 10 mg. of active ingredient per dosage unit.

46. Compositions as claimed in claim 43 for administration to children and babies, containing 0.1 to 5 mg. of active ingredient per dosage unit.

47. Compositions as claimed in claim 46 containing 0.5 to 2 mg. of active ingredient per dosage unit.

48. Compositions as claimed in any of claims 42 to 47 in the form of dragees, capsules, depot-dragees, suppositories or ampoules.

49. Compositions as claimed in claim 42 in the form of syrups or drop solutions.

50. Compositions as claimed in any of claims 42 to 49 which contain, in addition to the compounds of formula I, one or more further substances having analgesic, anti-inflammatory, anti - tussive, coronary - dilating or heart-stimulant activity.

51. Compositions as claimed in claim 42 substantially as herein described.

52. Compositions as claimed in claim 42 substantially as herein described with reference to any of Examples A—D.

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